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Schizophrenia and the Retina: Towards a 2020 Perspective

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Abstract

Background—Differences between people with schizophrenia and psychiatrically healthy controls have been consistently demonstrated on measures of retinal function such as electroretinography (ERG), and measures of retinal structure such as optical coherence tomography (OCT). Since our 2015 review of this literature, multiple new studies have been published using these techniques. At the same time, the accumulation of data has highlighted the "fault lines" in these fields, suggesting methodological considerations that need greater attention in future studies.

Methods—We reviewed studies of ERG and OCT in schizophrenia, as well as data from studies whose findings are relevant to interpreting these papers, such as those on effects of the following on ERG and OCT data: comorbid medical conditions that are over-represented in schizophrenia, smoking, antipsychotic medication, substance abuse, sex and gender, obesity, attention, motivation, and influences of brain activity on retinal function.

Results—Recent ERG and OCT studies continue to support the hypothesis of retinal structural and functional abnormalities in schizophrenia, and suggest that these are relevant to understanding broader aspects of pathophysiology, neurodevelopment, and neurodegeneration in this disorder. However, there are differences in findings which suggest that the effects of multiple variables on ERG and OCT data need further clarification.

Conclusions—The retina, as the only component of the CNS that can be imaged directly in live humans, has potential to clarify important aspects of schizophrenia. With greater attention to

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Contributors

Steven Silverstein conceived of the paper idea and wrote multiple sections of the manuscript, especially the sections related to critical issues in the field. Samantha Fradkin conducted the literature review of the recent ERG and OCT studies and wrote those sections of the paper. Docia Demmin conducted a portion of the literature review for the critical issues in the field sections and assisted with writing those sections.

Conflicts of Interest

The authors declare that they have no conflict of interest or perceived conflict of interest related to this work with any entity.

specific methodological issues, the true potential of ERG and OCT as biomarkers for important clinical phenomena in schizophrenia should become apparent.

Keywords

Schizophrenia; retina; electroretinography (ERG); optical coherence tomography (OCT); vision; perception; dopamine; histamine

1. Introductions

Many people with schizophrenia experience changes in visual perception. These include: 1) visual distortions such as temporary changes in the form, color, and brightness of objects, which have been estimated to occur in approximately 2/3 of patients (Bunney et al., 1999; Cutting and Dunne, 1986; Keane et al., 2018; Phillipson and Harris, 1985); 2) visual hallucinations, which have been estimated to occur in approximately 1/3 of patients (Waters et al., 2014), with some studies reporting significantly higher rates [e.g., 48% in (Keane et al., 2018)]; and 3) abnormalities on laboratory measures of visual processing, including on measures of low-level functions such as contrast sensitivity (Silverstein, 2016). A relatively unstudied question regarding these phenomena is the extent to which these changes involve alterations in retinal function, as opposed to only changes in cortical and subcortical function, as is typically assumed. There are at least four reasons why this is an important question. First, many aspects of impaired low-level visual processing in schizophrenia (e.g. in contrast sensitivity, color perception), and some of the types of visual distortions and hallucinations reported by patients, are similar to what is observed in other conditions with known retinal impairments (e.g., Parkinson's disease, retinal dystrophies) (Archibald et al., 2009; Brandies and Yehuda, 2008; Ffytche, 2007, 2009; Silverstein et al., 2017b; Silverstein and Rosen, 2015; Witkovsky, 2004). Second, impaired functioning as early as the retina would cause weaker signaling at the subcortical and possibly cortical levels, and this could have multiple serious consequences including: a lowered signal-to-noise ratio (i.e., noisier representations); increased entropy/uncertainty regarding the nature of signals and greater subsequent demands on perceptual decision making, compensatory effects such as development of excessive overlap between receptive fields (i.e., broadening of neural tuning); slowness of processing (to reduce errors); and excessive amplification of sensory signals, but also noise, at the cortical level (Linsker, 1988; Silverstein et al., 2017a; Silverstein et al., 2017c). Third, the retina is a part of the central nervous system (CNS) that grows out of the same tissue as the brain early in development, and shares many features of the brain (e.g., use of the same neurotransmitters and receptor types, multiple forms of neurons and glial cells, lateral connectivity, feedback connections) (Dowling, 2012), but is more accessible than the brain for study, and therefore could be useful in accelerating our understanding of CNS pathophysiology, and screening for it, in schizophrenia. Fourth, several other conditions (e.g., autism, aging, multiple sclerosis, Parkinson's disease, Lewy-body dementia, fronto-temporal dementia, Alzheimer's disease, mild cognitive impairment) involve both retinal and brain changes, with extent of retinal pathology often being predictive of illness severity and progression, and cognitive findings, in those conditions (Ascaso et al., 2014; Costello and Burton, 2018; Deal et al., 2018; Devos et al., 2005; Djamgoz et al., 1997; Ferrari et al., 2017; Jindal, 2015; Liu et al., 2015; Ong et al., 2015;

Roy et al., 1997; Satue et al., 2014; Sedighi et al., 2014; Tian et al., 2011; Yu et al., 2014; Zimmerman et al., 2014), raising the possibility that similar predictive relationships might be observed in schizophrenia. For all of these reasons, the study of vision, and of retinal function in particular, is a promising approach to clarifying multiple aspects of the disorder. Despite this promise, however, it is a curious fact that while vision is the most studied and understood area of neuroscience, it is studied far less than other forms of neural computation (e.g., executive function, memory, attention, etc.) in schizophrenia (Silverstein and Keane, 2011). And, in the history of research on visual function in schizophrenia, studies of retinal structure and function make up less than 2% of all studies of visual perception in schizophrenia, based on a review of PubMed citations.

Early studies of this issue were few and far between (Balogh et al., 2008; Gagrat et al., 1979; Gerbaldo et al., 1992; Marmor et al., 1988; Schechter et al., 1987; Warner et al., 1999). It is only in the last decade that studies reporting altered retinal structure (Ascaso et al., 2010; Ascaso et al., 2015; Cabezon et al., 2012; Celik et al., 2016; Chu et al., 2012; Joe et al., 2018; Lee et al., 2013; Samani et al., 2018; Schonfeldt-Lecuona et al., 2019; Silverstein et al., 2018; Vincent et al., in press; Yilmaz et al., 2016) and function (Demmin et al., in press; Demmin et al., 2018; Gagné et al., in press; Hebert et al., 2010; Hebert et al., in press; Hebert et al., 2015) in people with, or at risk for, schizophrenia, or in relevant animal models (Lavoie et al., 2014a; Lavoie et al., 2014b), have begun to appear more regularly. In addition, multiple reviews on abnormal retinal structure or function, or both, in schizophrenia have been published in the past 5 years (Adams and Nasrallah, 2018; Gagne et al., 2015; Garcia-Portilla et al., 2019; Gracitelli et al., 2015; Hosak et al., 2018; Jerotić and Marić, 2018; Kazakos and Karageorgiou, in press; Lavoie et al., 2014c; Lizano et al., in press; Pan et al., 2018; Schonfeldt-Lecuona et al., 2016; Schwitzer et al., 2016; Silverstein and Rosen, 2015). Other reviews, not focused exclusively on schizophrenia spectrum conditions, also demonstrate the relevance of retinal changes to schizophrenia, and in some cases to visual processing changes and symptoms such as visual hallucinations (Bernardin et al., 2017; Chhablani et al., 2018). In 2015, we published a review of ocular (primarily retinal) issues in schizophrenia (Silverstein and Rosen, 2015) that covered the then-available literature on changes in retinal structure as measured by optical coherence tomography (OCT), function as measured by electroretinography (ERG), and vasculature as measured by fundus photography [e.g., (Meier et al., 2015; Meier et al., 2013)]. The purpose of the present review is twofold: 1) To provide an up-to-date review of studies of retinal structure and function in schizophrenia; and 2) To address issues not raised in earlier reviews but which can now be seen to be critical to future discovery in this field (e.g., effects of comorbid systemic medical conditions, smoking, medication, substance abuse, sex and gender, obesity, attention, motivation, and retinopetal/centrifugal influences). To perform this review, a search for relevant studies was conducted using PubMed, the reference sections of all studies identified from that search, and the reference sections of all studies cited in our 2015 review. For the PubMed search, the following keywords were used: schizophrenia, retina, optical coherence tomography (OCT), electroretinography (ERG), retinal nerve fiber layer (RNFL), macula, ganglion cell layer, inner plexiform layer, and cup-to-disc ratio. We begin with a review of OCT studies of retinal structure, followed by ERG studies of retinal function, and we then conclude by discussing methodological considerations.

2. Optical coherence tomography studies of schizophrenia

Multiple studies have reported retinal structural abnormalities among individuals with schizophrenia using OCT. Most of these studies focused on retinal nerve fiber layer (RNFL) thinning, which represents a reduction in ganglion cell axons, and macular volume (MV), which reflects thinning of the fovea and surrounding tissue, typically between the inner limiting membrane and the retinal pigment epithelium. From the beginning of research in this field, studies found that individuals with schizophrenia demonstrated reductions in both RNFL thickness and MV (Lee et al., 2013) or only RNFL thickness (Ascaso et al., 2010; Cabezon et al., 2012). One of the first studies of this issue (Chu et al., 2012) did not find significant overall RNFL or MV thinning in schizophrenia, but found an association between reduction in MV and positive symptoms. That study used an older OCT method (time domain OCT) with weaker resolution (~10 micron axial resolution with 400 axial scans per second), whereas more recent studies used the newer spectral domain OCT method, with ~5 micron resolution and over 25,000 axial scans per second.

Consistent with prior studies, Ascaso et al. (2015) found reductions in RNFL thickness, macular inner ring thickness, and MV in individuals with schizophrenia compared to controls. After patients were separated into recent illness episode (RIE) and non-recent illness episode (NRIE) groups, only NRIE patients demonstrated reduced retinal thickness in all parameters. The authors suggested this might be due to neuroinflammation and edema that can occur during an acute illness episode and that can mask evidence of tissue loss [as in MS (Kaufhold et al., 2013)]. Additionally, there were no associations between OCT measures and total illness duration. Yilmaz et al. (2016) reported similar findings, including reduced overall and nasal peripapillary RNFL thickness, as well as reduced macular thickness in outer nasal and outer inferior macular areas, in schizophrenia. Celik et al. (2016) focused on the comparison between treatment refractory and treatment responsive schizophrenia patients and investigated RNFL, ganglion cell layer (GCL) and inner plexiform layer (IPL) thickness. They reported reduced right eye global RNFL thickness, as well as right temporo-superior and right temporo-inferior segment thinning among patients with schizophrenia in comparison to controls. Patients also demonstrated reductions in GCL and IPL volumes, and those classified as treatment resistant demonstrated lower GCL and IPL measurements than treatment responsive patients. In addition, choroidal thickness was significantly lower in the treatment resistant patients than treatment responsive patients, but there were no significant differences in choroidal thickness reported between overall patient and control groups. The authors suggested that this may be a result of longer disease duration and antipsychotic use in treatment resistant patients. The researchers also reported negative correlations between GCL and IPL thickness and disease parameters, including disease duration, symptom severity, and number of hospitalizations.

One of the only studies to investigate retinal layer thickness and its association with visual processing deficits in schizophrenia was conducted by Samani and colleagues (2018). In this study, reduced macular thickness in the foveal region, nasal parafoveal region, and temporal parafoveal region was observed in patients. Patients also demonstrated outer nuclear layer (ONL) and inner segment layer (ISL) thinning in multiple regions, which was related to negative symptom severity. Notably, reduced ganglion cell layer thickness in the temporal

parafoveal region in patients was associated with decreased low spatial frequency contrast sensitivity, which the authors suggest may reflect magnocellular ganglion cell loss throughout disease progression.

Another recent study looked at RNFL, macular, and subfoveal choroidal thickness (SFCT) in schizophrenia compared with controls (Topcu-Yilmaz et al., 2018). Although there were no significant differences in RNFL and SFCT thickness between groups, patients demonstrated macular thinning in multiple regions. RNFL and macular thickness were not associated with symptom severity or disease duration. However, patients in this study were recruited from an inpatient unit and were likely in an acute illness phase; therefore, as in Ascaso et al. (2015), the authors noted the possibility that RNFL thinning might masked by neuroinflammation. In another study that examined retinal layers not examined in most prior studies (Schonfeldt-Lecuona et al., 2019), significant differences between a combined schizophrenia-schizoaffective disorder group and controls were observed in macular volume, and macular, RNFL and inner nucleiform layer (INL) thickness. Moreover, this was the first study to find a significant inverse correlation between the duration of illness and an RNFL variable (total volume).

In a pilot study by Joe et al. (2018), patients with psychosis (schizophrenia or bipolar disorder; n=6) demonstrated, relative to controls (n=18), decreased macular thickness values in the inner ring immediately surrounding the central subfield, which was not correlated with duration of illness. A reduction in mean choroidal thickness in psychosis patients was also reported, but this finding was not significant. However, the authors suggest this may have been a result of the small sample size.

In order to address potential confounding methodological factors in previous studies, Silverstein et al. (2018) studied the relationship between structural retinal factors in schizophrenia and comorbid medical conditions. No differences in RNFL or macula measurements were observed in the schizophrenia group in comparison to controls. However, when collapsing across patient and control groups, RNFL, macula, and GCL-IPL thinning were associated with diabetes and hypertension, conditions which have a higher prevalence in schizophrenia (Mamakou et al., 2018; Nishanth et al., 2017), and which are independently associated with retinal thinning (Gangwani et al., 2015; Spaide, 2019). Nonetheless, even after controlling for diabetes and hypertension, schizophrenia patients demonstrated enlarged optic cup volumes and cup-to-disc ratios, indicating a widening of the opening where the retinal ganglion cell axons exit the retina as the optic nerve, which is suggestive of tissue loss in the surrounding regions (Airaksinen and Alanko, 1983; Choi et al., 2014). This result replicated an earlier finding reported in a published conference abstract (Cabezon et al., 2012). Additional findings from this study were that larger left and right eye cup volumes were associated with higher Positive and Negative Syndrome Scale [PANSS; (Kay et al., 1987)] Cognitive symptom factor scores (Lindenmayer et al., 1994; Lindenmayer et al., 1995) and with antipsychotic medication dose. This may indicate that structural alterations, perhaps reflecting neural degeneration, observed at the point that the optic nerve leaves the retina, are associated with a more severe form of illness, including more cognitive impairment and the need for higher medication doses.

Vincent et al. (Vincent et al., in press) conducted the first intra-device reliability study of OCT in schizophrenia, using Spectralis and Cirrus devices. Patients demonstrated macula thinning on both devices, but not RNFL or GCL-IPL thinning. Reliability was good across machines but varied across measures as a function of device.

Overall, studies of OCT in schizophrenia consistently indicate evidence of structural retinal pathology. However, the sites of the abnormalities are often inconsistent across studies (i.e., RNFL, macula, optic nerve head), and while some evidence of normal findings has been attributed to recent illness episodes [and so possibly to neuroinflammation masking retinal atrophy] (Ascaso et al., 2015; Topcu-Yilmaz et al., 2018)], other studies reported normal findings in clinically stable patients [e.g., (Chu et al., 2012; Silverstein et al., 2018)]. Thus, OCT continues to show promise as a neuroimaging technique for schizophrenia. However, there are clearly a number of variables that affect what findings emerge, and it is not really clear at this point what all of those variables are, or even what the relative contributions are of the variables that we suspect may be relevant (e.g., different scanners, marijuana use, medication history, presence of diabetes, etc.). In the next section of the paper (following the review of recent ERG studies below), we discuss those factors that we believe are most relevant to gaining a better understanding of retinal degeneration in schizophrenia.

3. Electroretinography (ERG) studies of schizophrenia

Anomalies in retinal functioning in schizophrenia have been consistently observed in schizophrenia, in the form of changes in flash ERG waveforms and, in some cases, their implicit times or latencies (Lavoie et al., 2014b). In studies of schizophrenia, several waveforms have been assessed, including the a-wave of the flash fERG which reflects photoreceptor (rod and/or cone) response, the b-wave of the fERG which reflects combined activity of bipolar and Müller (glial) cells, oscillatory potentials [a series of small positive deflections on the ascending curve of the fERG b-wave that are thought to be initiated by dopaminergic inhibitory activity within amacrine cells, and then actually generated by bipolar cells (Wachtmeister, 1998)], the photopic negative response of the fERG which reflects activity of retinal ganglion cells, and the waveforms of the pattern electroretinogram (pERG), which reflect activity of retinal ganglion cells in response to stimuli with clearly defined borders between light and dark regions (Creel, 2012; Frishman et al., 2018; Perlman, 2012; Porciatti, 2015). Marmor et al. (Marmor et al., 1988) focused on oscillatory potentials and did not find abnormalities in these waveforms in schizophrenia patients, all of whom were unmedicated. Warner et al. (1999) found reduced cone a-wave and rod a- and b-wave amplitudes in individuals with schizophrenia, unrelated to medication dose, when compared to controls. Another study demonstrated decreased a-wave amplitudes in patients with schizophrenia following hospitalization for acute psychosis (Balogh et al., 2008). Notably, these abnormalities were partially normalized following 8 weeks of treatment, which suggested a possible state effect. Hébert et al. (2015) found reductions in cone a-wave amplitude, mixed rod-cone b-wave amplitude, and rod b-wave amplitude among individuals with schizophrenia (n=105), and lower rod b-wave amplitudes and longer latencies in unaffected offspring of parents with schizophrenia or bipolar disorder (Hebert et al., 2010), suggesting that the b-wave component may be sensitive to illness diathesis. These initial ERG findings suggested that acute psychosis may be characterized by abnormal

photoreceptor functioning, whereas aberrant bipolar-Müller cell functioning may occur in chronic schizophrenia and in high-risk individuals regardless of level of symptoms, although the role of antipsychotic medication use in further lowering amplitudes was left as a question in need of further study.

Recent studies of retinal functional activity in schizophrenia have reported findings consistent with those of previous studies in indicating that schizophrenia patients demonstrate attenuated photoreceptor and bipolar cell activity. Using a portable ERG device, Demmin et al. (2018) found decreased photoreceptor and bipolar cell activity in patients under both photopic and scotopic conditions at higher stimulus intensities, and using a flicker paradigm (further indicating impaired cone function). Patients also demonstrated attenuated photopic negative response (PhNR) amplitude, suggesting reduced retinal ganglion cell activity. There were no significant differences between patients and controls in implicit time of peak amplitudes on any test in this study. A consistent pattern of correlations also emerged indicating that weaker responses to the dimmest light stimuli in both photopic and scotopic conditions were related to higher levels of negative symptoms in patients.

We recently reported on the effects of a food reward on ERG indices measured at baseline, anticipation of reward, and immediately post-reward, in schizophrenia and healthy control groups (Demmin et al., in press). Consistent with previous ERG studies, a- and b-wave amplitudes were lower in the schizophrenia group when compared to controls. Interestingly, controls demonstrated differences in b-wave amplitude between each pairwise combination of the three conditions, with a linear decrease in amplitude as a function of increasing reward salience, while these differences were not seen in the schizophrenia group. For both groups, ERG amplitudes were related to indices of hedonic capacity, and they were related to negative symptoms involving motivation and hedonic capacity in patients. Differences in the direction of findings between the controls in this study and those in a prior study of food reward effects on ERG in controls (Nasser et al., 2013) are discussed in the next section, in the subsection on motivational effects on ERG data.

In the largest ERG study in psychiatry to date (Hebert et al., in press), flash ERG data were recorded in 150 schizophrenia patients, 151 bipolar disorder patients, and 200 psychiatrically healthy control subjects. Both disorders were characterized by reduced a-wave amplitudes, prolonged b-wave latencies, and reduced mixed rod-cone a- and b-wave amplitudes. Reduced cone b-wave amplitude was observed only in the schizophrenia group, however. In addition, the schizophrenia group could be differentiated from both the bipolar disorder and control groups with high levels of accuracy, sensitivity and specificity based on a combination of ERG metrics. Of note, ERG indices were not significantly correlated with antipsychotic medication dosages. These data provide the most convincing evidence to date of the potential of ERG to be useful as an aid in differential diagnosis – a utility that presumably could be refined further with additional studies including a wider range of ERG parameters and devices. The data of (Hebert et al., in press) demonstrates a translational utility that is often an expressed long-term goal of much research on perception and cognition in psychiatry, but that is rarely achieved.

In a follow up study to Hébert et al. (2010), flash ERG data (restricted to b-wave indices) were recorded in 99 offspring of parents with either schizophrenia, bipolar disorder, or major depressive disorder (mean age = 16.03, SD = 6.14) and compared to data from 223 age- and sex-matched psychiatrically healthy controls (Gagné et al., in press). Replicating past findings, this study found that in the high-risk group, rod b-wave amplitude was decreased, and rod and cone b-wave latencies were increased. The groups did not differ in cone b-wave amplitude, the latter being a metric that has been found to be abnormal in schizophrenia (Demmin et al., 2018; Hebert et al., 2015), but not in high risk subjects or people with mood disorders (Hebert et al., 2010; Hébert et al., 2017). This suggests that this metric may be linked to presence and/or severity of psychosis, which is consistent with the known sensitivity of cones, especially those sensitive to blue light, to dopamine levels in the brain and retina (Brandies and Yehuda, 2008; Demmin et al., in press; Lavoie et al., 2014b; Nasser et al., 2013; Popova, 2014; Popova et al., 2016; Roy et al., 1997; Roy et al., 1996; Witkovsky, 2004).

In a study focused on retinal ganglion cell activity, Moghimi et al. (in press) replicated the finding of attenuated PhNR amplitudes in schizophrenia, originally reported in Demmin et al. (2018). They also observed multiple trend-level findings on the pattern ERG suggestive of impairment in schizophrenia. Due to the small sample size, large variability in performance among patients, and sex differences in performance, the meaning and implications of these findings need to be explored further. If they can be replicated in larger samples, however, the data could guide studies to answer questions such as: 1) which of the many types of ganglion cells are most affected in schizophrenia?; 2) to what extent do impairments in specific types of retinal cells (e.g., midget vs. parasol cells) differentially contribute to the well-characterized ventral and dorsal stream cortical disturbances in visual processing in schizophrenia?; 3) to what extent do findings on retinal cell types point towards specific genetic contributions to schizophrenia; and 4) in the development and course of schizophrenia, do changes in retinal ganglion cell function occur in parallel with, or earlier or later than, bipolar-Müller cell and photoreceptor changes? The last question is relevant to the hypothesis that some proportion of structural and functional changes of the retina in schizophrenia may be due to retrograde trans-synaptic degeneration, in which loss of occipital lobe volume leads to death of cells projecting to this region from the lateral geniculate nucleus (LGN), which leads to death of ganglion cells (which project to the LGN), and perhaps eventually to changes in earlier layers such as the outer nuclear layer (the location of bipolar cell bodies) and the photoreceptor layer (Silverstein et al., 2018). It is also possible, however, that changes progress in the other direction (anterograde trans-synaptic degeneration), in which death of retinal cells leads to changes in the LGN and then eventually to volume loss in the visual cortex. At present, the relative timing of functional and structural changes in different retinal layers in schizophrenia has not been explored.

4. Critical issues

4.1 Systemic disease effects

In our view, one of the most important, and typically unaddressed issues in this field involves the extent to which abnormal retinal findings in studies such as those cited above

are due to schizophrenia, as opposed to being effects of comorbid diseases. Two such conditions are diabetes or hypertension. Both of these conditions are over-represented, underdiagnosed, and undertreated in people with schizophrenia (Bernardo et al., 2009; Correll et al., 2014; Hoffman, 2017), both are associated with brain pathology including cognitive impairment (Parfenov et al., 2018; Zilliox et al., 2016), and their presence is associated with poorer cognitive functioning in people with schizophrenia relative to people with schizophrenia without these conditions (Dickinson et al., 2008; Morra and Strauss, 2016). Diabetes (both Type I and II) and hypertension also have negative effects on retinal health (Modi and Arsiwalla, 2018; Yasin Alibhai et al., 2018), including significant thinning of retinal layers as indicated by OCT (Chhablani et al., 2015; Chhablani et al., 2018; Dumitrescu et al., 2017; Wang et al., 2015), and impairments in retinal function as indicated by ERG (Bellini et al., 1995; Gundogan et al., 2008; Lecleire-Collet et al., 2011; Parisi and Uccioli, 2001; Ravalico et al., 1995; Tyrberg et al., 2011), even in the absence of diagnosable retinopathy. Therefore, excluding people with, for example, diabetic retinopathy, from studies of the retina in schizophrenia is not sufficient to guard against the effects of systemic disease [see (Yasin Alibhai et al., 2018; Zeng et al., in press) for two good recent examples of this in non-psychiatric studies]. We demonstrated this in a recent study from our lab, as noted above, in which we observed that when schizophrenia patients free of diabetes or hypertension were compared to controls free of these conditions, there were no differences in RNFL, macula, or GCL-IPL thickness values (Silverstein et al., 2018). In contrast, when all subjects with diabetes or hypertension were compared to all subjects without these diseases (combined across the schizophrenia and healthy control groups) there were many variables where the diabetes-hypertension group demonstrated evidence of retinal thinning. Therefore, studies of retinal structure and function in schizophrenia that do not include presence of diabetes and hypertension (and other relevant diseases that can affect the eye) as independent variables may erroneously conclude that there is a direct schizophrenia-related effect in cases when none exists.

4.2 Smoking

Another relatively neglected issue in research on perception and cognition in schizophrenia is the effects of chronic smoking. Regarding the retina specifically, nicotine is known to cross the blood-retina barrier (Tega et al., 2015) and to reduce (either initially, or secondary to inhibition after an initial increase in activity, depending on the condition) ERG amplitudes (Varghese et al., 2011). Because estimates of smoking in schizophrenia are often at around 80% (de Leon and Diaz, 2005; Dervaux and Laqueille, 2008; Williams and Gandhi, 2008), and it has been shown that people with schizophrenia absorb more nicotine per cigarette than people without schizophrenia (Williams et al., 2010), this raises the possibility that smoking plays a significant role in the reduced ERG amplitudes found in people with schizophrenia. Smoking has also been associated with thinning of retinal structures such as the retinal nerve fiber layer (El-Shazly et al., 2017; Kucuk and Akkaya, 2018; Teberik, 2019), although this has not always been found (Rosso et al., 2019). These data raise the question of how much of the retinal structural and functional changes found in schizophrenia are due to smoking effects.

4.3 Medication

The overwhelming majority of studies of schizophrenia have involved medicated patients, which renders difficult the interpretation of the extent to which reduced a- and b-wave amplitudes in the fERG are due to medication effects and/or to schizophrenia. This is an important issue because: 1) data from healthy controls indicates that chlorpromazine, and to a lesser extent haloperidol, lowers ERG amplitudes and prolongs latencies in healthy people, and does so significantly more than a benzodiazepine, anticholinergic drugs, or placebo (Bartel et al., 1990a, b; Bartel et al., 1990c); and 2) ERG assessment in the same schizophrenia patients from acute hospitalization (an average of 4.6 weeks after starting medication) to 8 weeks later indicated that a-wave amplitude was no longer significantly different than among controls after the follow-up period [note that this was one of the only studies that did not show attenuated b-wave amplitudes in patients (see also (Warner et al., 1999)]. Therefore, medication status and duration may need further attention in future studies. It is likely, however, that some findings may be diathesis/trait/disease-related, such as those of Hébert et al. (2010) and Gagné et al. (in press) who found ERG anomalies in healthy offspring of a parent with a serious mental illness, as described above.

The mechanism of medication effects is likely to involve passage through the blood-retina barrier (BRB). Blood is supplied to the retina from two sources: the central retinal artery which is located in the center of the optic nerve bundle, and which branches into capillaries in the inner retina, and the choroid which supplies blood to the outer retinal cells and photoreceptors. There are actually two types of BRBs: 1) tight junctions between retinal capillary endothelial cells (the inner BRB; and 2) tight junctions between retinal pigment epithelilial cells (the outer BRB) (Cunha-Vaz et al., 2011). Medications vary widely in their ability to pass through the BRB, and the permeability of most antipsychotic medications is not known, since it is medications to treat retinal diseases that are typically studied. However, many drugs, including some that have been commonly used in psychiatry (e.g., verapamil) easily cross the BRB (Hosoya et al., 2011), and L-DOPA, which affects retinal function (Brandies and Yehuda, 2008) does so as well. Because antipsychotic medications cross the blood-brain barrier, and can cause cytotoxic effects and death of endothelial cells in the brain, leading to unwanted increases in permeability (Elmorsy et al., 2014), further study of antipsychotic medication effects in ERG studies is warranted, especially regarding whether cytotoxic effects on *retinal* endothelial cells can occur due to these medications. Much less is known about medication effects on OCT findings, but preliminary evidence suggests that at least some antipsychotic medications can have negative effects on retinal structures. For example, clozapine or fluphenazine use can lead to maculopathy (Lee and Fern, 2004; Tong et al., 2017), and aripiprazole and thioridazine use have been linked to chorioretinopathy (Connell et al., 1964; Faure et al., 2015; Meredith et al., 1978; Neves et al., 1990). Therefore, it is possible that some of the OCT findings in schizophrenia could reflect toxic effects of antipsychotic medications on neural and/or vascular structures within the retina. Another important question is the extent to which data suggesting that retinal thinning is associated with increased illness chronicity (Ascaso et al., 2015; Lee et al., 2013) reflects an actual illness progression effect, as opposed to these toxic effects, or to effects of chronic blockade of DA receptors in the retina, which could lead to reductions of dendrites and axonal and cell death (Silverstein and Rosen, 2015). A further caveat here is that illness

chronicity, and lifetime exposure to antipsychotic medication, are highly likely to be related to age in any patient sample, which introduces a further confound since age is related to thinning of retinal structures (Ryoo et al., 2018). The importance of this can be seen in the difference between the Lee et al. (2013) study, which found a relationship between OCT variables and illness chronicity but did not control for age, and the study of Ascaso et al. (2015), which did not find a relationship with illness duration but did control for age.

4.4 Substance Use

The rate of comorbid substance use disorders in people with schizophrenia has been estimated to be over 40% (Hunt et al., 2018). People with significant substance use are typically excluded from studies of perception and cognition in schizophrenia. Beyond the issue of generalizability of findings when 40% of people with a condition are excluded from studies, there are many people who do not meet criteria for a substance use disorder but who have drugs in their bloodstream. This is increasingly becoming a problem with legalization of cannabis. Cannabis use is associated with noisier signals in the flash ERG (Lucas et al., 2019), and delayed signals in both the flash ERG (Schwitzer et al., 2018) and pattern ERG (Schwitzer et al., 2017), the latter a technique that is just starting to be used in studies of schizophrenia [e.g., (Moghimi et al., in press)]. ERG effects as the result of chronic cocaine use and withdrawal (Roy et al., 1997; Roy et al., 1996; Sanchez-Villarejo et al., 2014), chronic alcohol use in animal studies (Sancho-Tello et al., 2008), and other forms of drug abuse (Su et al., 2017; Toyonaga et al., 1989) have also been reported. Therefore, it is important to isolate, as much as possible, effects of schizophrenia from those of comorbid substance use in future ERG studies. Effects of substance use on retinal structure are less clear at this point, but case studies suggest the potential for structural changes (Su et al., 2017), and so an issue for future studies is to quantify the contribution of comorbid drug use, especially chronic use, in OCT studies.

4.5 Sex and gender

Schizophrenia is associated with sex (Mendrek and Mancini-Marie, 2016) and gender (Lewine et al., 2017) differences on multiple variables related to brain and cognition. For the most part, however, any such differences in ERG or OCT data in people with schizophrenia have been unreported, or studies were too small to have adequate power to reach definitive conclusions. However, sex differences in ERG data are well-established, with amplitudes reported to be significantly higher in women (Birch and Anderson, 1992; Brule et al., 2007; Karpe et al., 1950). Menstrual cycle phase effects on the ERG have also been studied. Brûlé et al. (2007) reported that whereas photopic ERG amplitudes were consistently larger in premenopausal women compared to men regardless of cycle phase, sex-differences on scotopic testing were observed only during the follicular phase. Hormonal effects on ERG data have also been shown in animal models (Chaychi et al., 2015). The data on sex differences in retinal structure are less clear but there is evidence that females have thicker RNFLs whereas males have thicker outer nuclear layer, outer plexiform layer, inner nuclear layer, and macular values (Ooto et al., 2011; Ryoo et al., 2018). Finally there is evidence from animal studies for estrogen receptors in multiple retinal layers, which could have neuroprotective and modulatory effects (Kobayashi et al., 1998) as long as significant levels of estrogen are present. All of these data suggest that sex differences should always be

reported in studies of retinal structure and function in schizophrenia, and that data from female subjects, at least for scotopic ERG findings, are best examined as a function of menstrual cycle phase.

4.6 Obesity

A recent study demonstrated that obesity is associated with thinning of the RNFL overall and in several of its subregions (Laiginhas et al., 2019). This is relevant to the present review because schizophrenia is associated with metabolic syndrome, weight gain, and obesity (McDaid and Smyth, 2015), even at the first episode (Correll et al., 2014). Although a significant degree of weight gain in even young people with schizophrenia is related to antipsychotic medication use (Theisen et al., 2001), weight gain in the disorder can be due to a number of factors (Dayabandara et al., 2017). Therefore, it will be important to examine the relationships between weight and OCT variables in future studies, and to control for this when appropriate (i.e., when it does not remove variance in the dependent measures that is associated with schizophrenia [see (Miller and Chapman, 2001)].

4.7 Attention

Given the well-known attentional impairment that is found in most people with schizophrenia (Seidman and Mirsky, 2017), understanding potential effects of reduced attention on ERG amplitudes is an important issue. Studies on this issue in healthy subjects have yielded mixed results, with some studies indicating no effect on ERG data (Hackley et al., 1990; Mangun et al., 1986), and other studies indicating that b-wave amplitudes were larger for stimuli in an attended vs. an unattended visual field [(Eason, 1984; Eason et al., 1983) reviewed in (Ortiz et al., 2017)]. At this point, we recommend that future studies add an attentional manipulation when possible, given the potential for attentional effects to be present at least under some conditions.

It is also important to note that the vigilance level, or attentiveness, of the subject impacts the pupil size significantly (Reimer et al., 2016), and therefore the ERG values under conditions of constant stimulus luminance. Because people with schizophrenia, especially those with negative symptoms, can demonstrate reduced pupil sizes (Granholm and Verney, 2004; Minassian et al., 2004; Thakkar et al., 2018; Verney et al., 2004), if this variable is not taken into account in statistical analyses of between-group effects, the impact of the attentional state may lead to false interpretations.

4.8 Motivation and retinopetal influences

Effects of food reward on ERG amplitudes in humans have been demonstrated in two studies (Demmin et al., in press; Nasser et al., 2013). This suggests that the overall motivational state of the subject (caused either by anticipating a reward, or immediately after consuming a reward), and perhaps overall arousal level, may influence ERG data. We discussed this issue in detail in Demmin et al. (in press) and so here will only summarize the most general issues raised by this line of research. Most importantly, fast-acting central effects such as changes in b-wave amplitude immediately after consuming a food reward are unlikely to be due to activity at the blood-retina barrier. Rather, such effects are likely to involve activity of retinopetal (or centrifugal, or efferent) neurons: those that enter the retina from the brain

through the optic nerve bundle, and that modulate the responses of retinal cells. These neurons are few in number, but are characterized by extensive branching inside the retina, where they affect multiple aspects of retinal function. To date, the only known retinopetal neurons are histaminergic and serotinergic (Gastinger et al., 2006; Labandeira-Garcia et al., 1990; Ortiz et al., 2017). Several lines of evidence suggest that the food reward effects observed in the studies cited above are related to histaminergic effects. For example, the primary source of histaminergic retinopetal neurons in humans is thought to be the hypothalamus (Gastinger et al., 2006; Ortiz et al., 2017), where activation in response to food reward has been demonstrated many times (Anand and Brobeck, 1951; Qualls-Creekmore et al., 2017; Uribe-Cerda et al., 2018). Second and related to the prior point, brain histamine release is increased in the presence of food reward (Torrealba et al., 2012). Third, histamine is also involved more generally in promoting arousal, wakefulness, and attention (Ma et al., 2018), and this is relevant to presentation of a food reward, over and above the primary reinforcing effects of such a reward. Fourth, retinal histamine affects activity in on-center bipolar cells (Yu et al., 2009), and histamine receptors are found on cones, horizontal cells, and amacrine cells (Vila et al., 2012). Fifth, brain DA level changes (which contribute significantly to motivation) can affect histamine release (Horner et al., 2007; Yanovsky et al., 2011). These data broadly imply that ERG data may be affected by a person's motivation to perform and to complete the task, as well as possibly to their overall arousal level during the task. Since many schizophrenia patients are characterized by motivational disturbances (including in the representation and valuation of rewarding stimuli) (Catalano et al., 2018; Fervaha et al., 2013; Schlosser et al., 2014; Strauss et al., 2014; Subramaniam et al., 2015), it will be important to determine the extent to which findings of reduced retinal cell activity in schizophrenia reflect a primary anomaly in retinal cell signaling versus reduced modulatory effects from brain motivational systems. In general, clarifying attention and motivation effects in the ERG will help to generate a more refined estimate of the integrity of retinal cell function, while at the same time clarifying the extent to which ERG be viewed as a proxy for brain activity in schizophrenia, as has sometimes been the case with ERG in other disorders such as Parkinson's disease [reviewed in (Brandies and Yehuda, 2008)].

5. Conclusions

Studies published since our 2015 review continue to provide evidence for abnormalities of retinal function (using ERG) and structure (using OCT) in schizophrenia. Despite the convergence of most findings to date, there remain a number of issues that can now be seen as clearly relevant to moving forward with this line of research. These include influences of the following on retinal structure and function in schizophrenia: 1) systemic disease, especially diabetes and hypertension; 2) smoking; 3) antipsychotic medication; 4) substance use; 5) sex and gender; 6) obesity, 7) attention; and 8) arousal and motivation, as they influence the retina via histaminergic and serotonergic input from brain regions. As there is suggestive but still little evidence about each of these issues, mechanistic studies in healthy controls are needed in addition to, and ideally prior to, studies in patients. Issues for which there is essentially no evidence in the literature, but that are also relevant to studies of people

with schizophrenia include effects of sleep disturbance, excessive caffeine use, trauma histories, anxiety and stress, and post-traumatic stress disorder symptoms, to name a few.

In addition to an increased attention to the above issues, several other methodological issues are relevant. One is determination of the optimal parameters of light stimuli (e.g., intensity, color, duration, background lighting characteristics) in ERG tests, in terms of achieving the greatest sensitivity to different clinical issues in schizophrenia (e.g., conversion to psychosis, differential diagnosis, medication response, impending relapse, potential for recovery). Another is the choice of outcome metrics for ERG studies. Traditionally, studies have focused on a- and b-wave amplitudes and latencies. There are other wave forms (e.g., c-wave, oscillatory potentials) that are likely to be informative, however, one of which, the photopic negative response, reflecting an aspect of ganglion cell response, was found to be abnormal in two recent studies (Demmin et al., 2018; Moghimi et al., in press). Beyond traditional waveforms, however, other approaches to ERG data analysis may be useful. These include examining the extent to which people with schizophrenia are characterized by less consistency in their responses from trial to trial at all points in the curves defining the traditional ERG waveforms (i.e., reduced intraclass correlation), and also the extent to which they may differ in the spectral frequency components of the individual waveforms at all or some timepoints [see (Gauvin et al., 2014; Gauvin et al., 2015) for examples of this approach].

Regarding OCT, there has been inconsistency in findings across studies of schizophrenia in terms of whether RNFL, macula, GCL-IPL or other structures showed abnormalities. One issue here is that most past studies have been too small to generate a strong estimate of between-group differences. Another is that in many cases, specific variables were not taken into account (e.g., antipsychotic medication dose and lifetime exposure, smoking, diabetes presence) that could have helped interpret the positive/negative findings within and across studies. And, as Vincent et al. (in press, this issue) demonstrated, somewhat different results may be obtained on different OCT scanners. State-related issues may also be relevant to OCT data, given recent findings that RNFL thickness increased after ECT treatment in a mixed psychiatric diagnosis sample (Ucar et al., 2018), and the suggestion that acute psychosis is associated with neuroinflammation that masks retinal thinning (see above). Ultimately, larger studies that address a wider range of patient variables will allow for more precise estimates of the sensitivity of different OCT indices to a range of schizophrenia-related outcomes. Recent advances in OCT angiography are also allowing for quantification of retinal blood vessel width, and so it will be useful to compare results from this method with those of semi-automated scoring methods applied to fundus photography images, which is now the standard in psychiatric studies of retinal vessel caliber [e.g., (Hill et al., in press)]. Finally, recent findings linking specific genetic loci to both macular thickness and to schizophrenia (Gao et al., 2019) point towards the potential future utility of including OCT variables in personalized medicine efforts at schizophrenia risk prediction.

Addressing the issues raised in the last two paragraphs is relevant both for better estimation of the nature and extent of retinal functional and structural pathology in schizophrenia, and for more accurate understanding of the meaning of longitudinal changes in ERG and OCT data in the same patients (i.e., the extent to which they may be state-related vs. illness

progression-related). Given the speed, tolerability, and low-cost of ERG and OCT assessments, especially relative to techniques such as fMRI or PET, there is real translational potential for including retinal assessments in ongoing screening, treatment and monitoring efforts for people with schizophrenia.

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References

Adams SA, Nasrallah HA, 2018 Multiple retinal anomalies in schizophrenia. Schizophr Res 195, 3–12. [PubMed: 28755877]

Airaksinen PJ, Alanko HI, 1983 Effect of retinal nerve fibre loss on the optic nerve head configuration in early glaucoma. Graefes Arch Clin Exp Ophthalmol 220(4), 193–196. [PubMed: 6884783]

Anand BK, Brobeck JR, 1951 Hypothalamic control of food intake in rats and cats. Yale J Biol Med 24(2), 123–140. [PubMed: 14901884]

Archibald NK, Clarke MP, Mosimann UP, Burn DJ, 2009 The retina in Parkinson's disease. Brain 132(Pt 5), 1128–1145. [PubMed: 19336464]

Ascaso FJ, Cabezon L, Quintanilla MA, Galve LG, Lopez-Anton R, Cristobal JA, Lobo A, 2010 Retinal nerve fiber layer thickness measured by optical coherence tomography in patients with schizophrenia: A short report. European Journal of Psychiatry 24(4), 227–235.

Ascaso FJ, Cruz N, Modrego PJ, Lopez-Anton R, Santabarbara J, Pascual LF, Lobo A, Cristobal JA, 2014 Retinal alterations in mild cognitive impairment and Alzheimer's disease: an optical coherence tomography study. Journal of neurology 261(8), 1522–1530. [PubMed: 24846203]

Ascaso FJ, Rodriguez-Jimenez R, Cabezon L, Lopez-Anton R, Santabarbara J, De la Camara C, Modrego PJ, Quintanilla MA, Bagney A, Gutierrez L, Cruz N, Cristobal JA, Lobo A, 2015 Retinal nerve fiber layer and macular thickness in patients with schizophrenia: Influence of recent illness episodes. Psychiatry Res 229(1–2), 230–236. [PubMed: 26213374]

Balogh Z, Benedek G, Keri S, 2008 Retinal dysfunctions in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 32(1), 297–300. [PubMed: 17889979]

Bartel P, Blom M, Robinson E, van der Meyden C, Sommers DK, Becker P, 1990a The effects of levodopa and haloperidol on flash and pattern ERGs and VEPs in normal humans. Documenta ophthalmologica. Advances in ophthalmology 76(1), 55–64. [PubMed: 2078983]

Bartel P, Blom M, Robinson E, van der Meyden C, Sommers DK, Becker P, 1990b Effects of two anticholinergic drugs on electroretinograms and visual evoked potentials in healthy human subjects. Neuropsychobiology 24(4), 205–209. [PubMed: 2135712]

Bartel P, Blom M, Robinson E, Van der Meyden C, Sommers DO, Becker P, 1990c Effects of chlorpromazine on pattern and flash ERGs and VEPs compared to oxazepam and to placebo in normal subjects. Electroencephalogr Clin Neurophysiol 77(5), 330–339. [PubMed: 1697524]

Bellini G, Bocin E, Cosenzi A, Sacerdote A, Molino R, Solimano N, Ravalico G, 1995 Oscillatory potentials of the electroretinogram in hypertensive patients. Hypertension 25(4 Pt 2), 839–841. [PubMed: 7721441]

Bernardin F, Schwan R, Lalanne L, Ligier F, Angioi-Duprez K, Schwitzer T, Laprevote V, 2017 The role of the retina in visual hallucinations: A review of the literature and implications for psychosis. Neuropsychologia 99, 128–138. [PubMed: 28263800]

Bernardo M, Canas F, Banegas JR, Casademont J, Riesgo Y, Varela C, Group RS, 2009 Prevalence and awareness of cardiovascular risk factors in patients with schizophrenia: a cross-sectional study in a

low cardiovascular disease risk geographical area. Eur Psychiatry 24(7), 431–441. [PubMed: 19783126]

Birch DG, Anderson JL, 1992 Standardized full-field electroretinography. Normal values and their variation with age. Arch Ophthalmol 110(11), 1571–1576. [PubMed: 1444914]

Brandies R, Yehuda S, 2008 The possible role of retinal dopaminergic system in visual performance. Neurosci Biobehav Rev 32(4), 611–656. [PubMed: 18061262]

Brule J, Lavoie MP, Casanova C, Lachapelle P, Hebert M, 2007 Evidence of a possible impact of the menstrual cycle on the reproducibility of scotopic ERGs in women. Documenta ophthalmologica. Advances in ophthalmology 114(3), 125–134. [PubMed: 17273847]

Bunney WE Jr., Hetrick WP, Bunney BG, Patterson JV, Jin Y, Potkin SG, Sandman CA, 1999 Structured Interview for Assessing Perceptual Anomalies (SIAPA). Schizophr Bull 25(3), 577–592. [PubMed: 10478790]

Cabezon L, Ascaso F, Ramiro P, Quintanilla M, Gutierrez L, Lobo A, Cristobal J, 2012 Optical coherence tomography: a window into the brain of schizophrenic patients. Acta Ophthalmologica 90(S249).

Catalano LT, Heerey EA, Gold JM, 2018 The valuation of social rewards in schizophrenia. J Abnorm Psychol 127(6), 602–611. [PubMed: 30102066]

Celik M, Kalenderoglu A, Sevgi Karadag A, Bekir Egilmez O, Han-Almis B, Simsek A, 2016 Decreases in ganglion cell layer and inner plexiform layer volumes correlate better with disease severity in schizophrenia patients than retinal nerve fiber layer thickness: Findings from spectral optic coherence tomography. Eur Psychiatry 32, 9–15. [PubMed: 26800301]

Chaychi S, Polosa A, Lachapelle P, 2015 Differences in Retinal Structure and Function between Aging Male and Female Sprague-Dawley Rats are Strongly Influenced by the Estrus Cycle. PLoS One 10(8), e0136056. [PubMed: 26317201]

Chhablani J, Sharma A, Goud A, Peguda HK, Rao HL, Begum VU, Barteselli G, 2015 Neurodegeneration in Type 2 Diabetes: Evidence From Spectral-Domain Optical Coherence Tomography. Invest Ophthalmol Vis Sci 56(11), 6333–6338. [PubMed: 26436886]

Chhablani PP, Ambiya V, Nair AG, Bondalapati S, Chhablani J, 2018 Retinal Findings on OCT in Systemic Conditions. Semin Ophthalmol 33(4), 525–546. [PubMed: 28640657]

Choi JA, Park HY, Shin HY, Park CK, 2014 Optic disc characteristics in patients with glaucoma and combined superior and inferior retinal nerve fiber layer defects. JAMA Ophthalmol 132(9), 1068–1075. [PubMed: 24921983]

Chu EM, Kolappan M, Barnes TR, Joyce EM, Ron MA, 2012 A window into the brain: an in vivo study of the retina in schizophrenia using optical coherence tomography. Psychiatry Res 203(1), 89–94. [PubMed: 22917503]

Connell MM, Poley BJ, McFarlane JR, 1964 Chorioretinopathy Associated with Thioridazine Therapy. Arch Ophthalmol 71, 816–821. [PubMed: 14133865]

Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, Marcy P, Addington J, Estroff SE, Robinson J, Penn DL, Azrin S, Goldstein A, Severe J, Heinssen R, Kane JM, 2014 Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. JAMA Psychiatry 71(12), 1350–1363. [PubMed: 25321337]

Costello F, Burton JM, 2018 Retinal imaging with optical coherence tomography: a biomarker in multiple sclerosis? Eye Brain 10, 47–63. [PubMed: 30104912]

Creel DJ, 2012 The electroretinogram and electro-oculogram: Clinical applications, in: Kolb H, Nelson R, Fernandez E, Jones B (Eds.), Webvision: The organization of the retina and visual system.

Cunha-Vaz J, Bernardes R, Lobo C, 2011 Blood-retinal barrier. Eur J Ophthalmol 21 Suppl 6, S3–9. [PubMed: 23264323]

Cutting J, Dunne F, 1986 The nature of the abnormal perceptual experiences at the onset of schizophrenia. Psychopathology 19(6), 347–352. [PubMed: 3615790]

Dayabandara M, Hanwella R, Ratnatunga S, Seneviratne S, Suraweera C, de Silva VA, 2017 Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. Neuropsychiatr Dis Treat 13, 2231–2241. [PubMed: 28883731]

de Leon J, Diaz FJ, 2005 A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res 76(2–3), 135–157. [PubMed: 15949648]

Deal JA, Sharrett AR, Rawlings AM, Gottesman RF, Bandeen-Roche K, Albert M, Knopman D, Selvin E, Wasserman BA, Klein B, Klein R, 2018 Retinal signs and 20-year cognitive decline in the Atherosclerosis Risk in Communities Study. Neurology 90(13), e1158–e1166. [PubMed: 29490915]

Demmin D, Mote J, Beaudette D, Thompson J, Silverstein S, in press Retinal functioning and reward processing in schizophrenia. Schizophrenia Research.

Demmin DL, Davis Q, Roche M, Silverstein SM, 2018 Electroretinographic anomalies in schizophrenia. J Abnorm Psychol 127(4), 417–428. [PubMed: 29745706]

Dervaux A, Laqueille X, 2008 [Smoking and schizophrenia: epidemiological and clinical features]. Encephale 34(3), 299–305. [PubMed: 18558153]

Devos D, Tir M, Maurage CA, Waucquier N, Defebvre L, Defoort-Dhellemmes S, Destee A, 2005 ERG and anatomical abnormalities suggesting retinopathy in dementia with Lewy bodies. Neurology 65(7), 1107–1110. [PubMed: 16217068]

Dickinson D, Gold JM, Dickerson FB, Medoff D, Dixon LB, 2008 Evidence of exacerbated cognitive deficits in schizophrenia patients with comorbid diabetes. Psychosomatics 49(2), 123–131. [PubMed: 18354065]

Djamgoz MB, Hankins MW, Hirano J, Archer SN, 1997 Neurobiology of retinal dopamine in relation to degenerative states of the tissue. Vision Res 37(24), 3509–3529. [PubMed: 9425527]

Dowling JE, 2012 The retina : an approachable part of the brain, Rev. ed. Belknap Press of Harvard University Press, Cambridge, Mass.

Dumitrescu AG, Istrate SL, Iancu RC, Guta OM, Ciuluvica R, Voinea L, 2017 Retinal changes in diabetic patients without diabetic retinopathy. Rom J Ophthalmol 61(4), 249–255. [PubMed: 29516043]

Eason RG, 1984 Selective attention effects on retinal and forebrain responses in humans: a replication and extension. Bulletin of the Psychonomic Society 22(4), 341–344.

Eason RG, Flowers L, Oakley M, 1983 Central neural influences on the human retina during selective attention. Physiological Psychology 11(1), 18–28.

El-Shazly AAE, Farweez YAT, Elewa LS, Elzankalony YA, Farweez BAT, 2017 Effect of Active and Passive Smoking on Retinal Nerve Fibre Layer and Ganglion Cell Complex. J Ophthalmol 2017, 6354025. [PubMed: 28491470]

Elmorsy E, Elzalabany LM, Elsheikha HM, Smith PA, 2014 Adverse effects of antipsychotics on micro-vascular endothelial cells of the human blood-brain barrier. Brain Res 1583, 255–268. [PubMed: 25139421]

Faure C, Audo I, Zeitz C, Letessier JB, Robert MP, 2015 Aripiprazole-induced chorioretinopathy: multimodal imaging and electrophysiological features. Documenta ophthalmologica. Advances in ophthalmology 131(1), 35–41. [PubMed: 25791769]

Ferrari L, Huang SC, Magnani G, Ambrosi A, Comi G, Leocani L, 2017 Optical Coherence Tomography Reveals Retinal Neuroaxonal Thinning in Frontotemporal Dementia as in Alzheimer's Disease. J Alzheimers Dis 56(3), 1101–1107. [PubMed: 28106555]

Fervaha G, Graff-Guerrero A, Zakzanis KK, Foussias G, Agid O, Remington G, 2013 Incentive motivation deficits in schizophrenia reflect effort computation impairments during cost-benefit decision-making. J Psychiatr Res 47(11), 1590–1596. [PubMed: 23992770]

Ffytche DH, 2007 Visual hallucinatory syndromes: past, present, and future. Dialogues in clinical neuroscience 9(2), 173–189. [PubMed: 17726916]

ffytche DH, 2009 Visual hallucinations in eye disease. Curr Opin Neurol 22(1), 28–35. [PubMed: 19165953]

Frishman L, Sustar M, Kremers J, McAnany JJ, Sarossy M, Tzekov R, Viswanathan S, 2018 ISCEV extended protocol for the photopic negative response (PhNR) of the full-field electroretinogram. Documenta ophthalmologica. Advances in ophthalmology 136(3), 207–211. [PubMed: 29855761]

Gagné A, Moreau I, St-Amour I, Marquet P, Maziade M, in press Retinal function anomalies in young offspring at genetic risk of schizophrenia and mood disorder: The meaning for illness pathophysiology. Schizophrenia Research.

Gagne AM, Hebert M, Maziade M, 2015 Revisiting visual dysfunctions in schizophrenia from the retina to the cortical cells: A manifestation of defective neurodevelopment. Prog Neuropsychopharmacol Biol Psychiatry 62, 29–34. [PubMed: 25934388]

Gagrat D, Maggiano J, Belmaker RH, 1979 Effect of neuroleptic treatment in schizophrenia on the electroretinogram, electrooculogram, and color vision. Psychiatry Res 1(1), 109. [PubMed: 298336]

Gangwani RA, Lee JW, Mo HY, Sum R, Kwong AS, Wang JH, Tsui WW, Chan JC, Lai JS, 2015 The Correlation of Retinal Nerve Fiber Layer Thickness With Blood Pressure in a Chinese Hypertensive Population. Medicine (Baltimore) 94(23), e947. [PubMed: 26061324]

Gao XR, Huang H, Kim H, 2019 Genome-wide association analyses identify 139 loci associated with macular thickness in the UK Biobank cohort. Human molecular genetics 28(7), 1162–1172. [PubMed: 30535121]

Garcia-Portilla MP, Garcia-Alvarez L, de la Fuente-Tomas L, Velasco-Iglesias A, Saiz PA, Gonzalez-Blanco L, Bobes Bascaran MT, Baamonde B, Alcalde I, Merayo-Lloves J, Bobes J, 2019 Could structural changes in the retinal layers be a new biomarker of mental disorders? A systematic review and thematic synthesis. Rev Psiquiatr Salud Ment.

Gastinger MJ, Tian N, Horvath T, Marshak DW, 2006 Retinopetal axons in mammals: emphasis on histamine and serotonin. Current eye research 31(7–8), 655–667. [PubMed: 16877274]

Gauvin M, Lina JM, Lachapelle P, 2014 Advance in ERG analysis: from peak time and amplitude to frequency, power, and energy. BioMed research international 2014, 246096. [PubMed: 25061605]

Gauvin M, Little JM, Lina JM, Lachapelle P, 2015 Functional decomposition of the human ERG based on the discrete wavelet transform. J Vis 15(16), 14.

Gerbaldo H, Thaker G, Tittel PG, Layne-Gedge J, Moran M, Demisch L, 1992 Abnormal electroretinography in schizophrenic patients with a history of sun gazing. Neuropsychobiology 25(2), 99–101. [PubMed: 1625783]

Gracitelli CP, Abe RY, Diniz-Filho A, Vaz-de-Lima FB, Paranhos A Jr., Medeiros FA, 2015 Ophthalmology issues in schizophrenia. Curr Psychiatry Rep 17(5), 28. [PubMed: 25773224]

Granholm E, Verney SP, 2004 Pupillary responses and attentional allocation problems on the backward masking task in schizophrenia. Int J Psychophysiol 52(1), 37–51. [PubMed: 15003371]

Gundogan FC, Isilak Z, Erdurman C, Mumcuoglu T, Durukan AH, Bayraktar MZ, 2008 Multifocal electroretinogram in mild to moderate essential hypertension. Clin Exp Hypertens 30(5), 375–384. [PubMed: 18633760]

Hackley SA, Woldorff M, Hillyard SA, 1990 Cross-modal selective attention effects on retinal, myogenic, brainstem, and cerebral evoked potentials. Psychophysiology 27(2), 195–208. [PubMed: 2247550]

Hebert M, Gagne AM, Paradis ME, Jomphe V, Roy MA, Merette C, Maziade M, 2010 Retinal response to light in young nonaffected offspring at high genetic risk of neuropsychiatric brain disorders. Biol Psychiatry 67(3), 270–274. [PubMed: 19833322]

Hebert M, Merette C, Gagne AM, Paccalet T, Moreau I, Lavoie J, Maziade M, in press The electroretinogram may differentiate schizophrenia from bipolar disorder. Biological Psychiatry.

Hebert M, Merette C, Paccalet T, Emond C, Gagne AM, Sasseville A, Maziade M, 2015 Light evoked potentials measured by electroretinogram may tap into the neurodevelopmental roots of schizophrenia. Schizophr Res 162(1–3), 294–295. [PubMed: 25579051]

Hébert M, Merette C, Paccalet T, Gagne AM, Maziade M, 2017 Electroretinographic anomalies in medicated and drug free patients with major depression: Tagging the developmental roots of major psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry 75, 10–15. [PubMed: 28007463]

Hill M, Wong T, Davis M, Meier M, in press Associations between cannabis use and retinal vessel diameter in young adults. Schizophrenia Research.

Hoffman RP, 2017 The Complex Inter-Relationship Between Diabetes and Schizophrenia. Curr Diabetes Rev 13(3), 528–532. [PubMed: 28000544]

Horner WE, Johnson DE, Schmidt AW, Rollema H, 2007 Methylphenidate and atomoxetine increase histamine release in rat prefrontal cortex. Eur J Pharmacol 558(1–3), 96–97. [PubMed: 17198700]

Hosak L, Sery O, Sadykov E, Studnicka J, 2018 Retinal abnormatilites as a diagnostic or prognostic marker of schizophrenia. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 162(3), 159–164. [PubMed: 29967563]

Hosoya K, Tomi M, Tachikawa M, 2011 Strategies for therapy of retinal diseases using systemic drug delivery: relevance of transporters at the blood-retinal barrier. Expert Opin Drug Deliv 8(12), 1571–1587. [PubMed: 22035231]

Hunt GE, Large MM, Cleary M, Lai HMX, Saunders JB, 2018 Prevalence of comorbid substance use in schizophrenia spectrum disorders in community and clinical settings, 1990–2017: Systematic review and meta-analysis. Drug and alcohol dependence 191, 234–258. [PubMed: 30153606]

Jerotić S, Marić NP, 2018 Structural retinal abnormalities as potential markers for psychosis spectrum disorders. Medicinski Podmladak 69(3), 41–47.

Jindal V, 2015 Interconnection between brain and retinal neurodegenerations. Molecular neurobiology 51(3), 885–892. [PubMed: 24826919]

Joe P, Ahmad M, Riley G, Weissman J, Smith RT, Malaspina D, 2018 A pilot study assessing retinal pathology in psychosis using optical coherence tomography: Choroidal and macular thickness. Psychiatry Res 263, 158–161. [PubMed: 29567341]

Karpe G, Rickenbach K, Thomasson S, 1950 The clinical electroretinogram. I. The normal electroretinogram above fifty years of age. Acta Ophthalmol (Copenh) 28(3), 301–305. [PubMed: 14846545]

Kaufhold F, Zimmman H, Schneider E, Ruprecht K, Paul F, Oberwahrenbrock T, Brandt A, 2013 Optic neuritis is associated with inner nuclear layer thickening and microcystic macular edema independently of multiple sclerosis. PLoS One 8(8), e71145. [PubMed: 23940706]

Kay SR, Fiszbein A, Opler LA, 1987 The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13(2), 261–276. [PubMed: 3616518]

Kazakos C, Karageorgiou V, in press Retinal changes in schizophrenia: A systematic review and meta-analysis based on individual participant data. Schizophr Bull.

Keane BP, Cruz LN, Paterno D, Silverstein SM, 2018 Self-Reported Visual Perceptual Abnormalities Are Strongly Associated with Core Clinical Features in Psychotic Disorders. Frontiers in psychiatry 9, 69. [PubMed: 29593580]

Kobayashi K, Kobayashi H, Ueda M, Honda Y, 1998 Estrogen receptor expression in bovine and rat retinas. Invest Ophthalmol Vis Sci 39(11), 2105–2110. [PubMed: 9761289]

Kucuk B, Akkaya S, 2018 The effect of smoking cessation on posterior ocular structures. Arquivos brasileiros de oftalmologia 81(5), 361–365. [PubMed: 30208136]

Labandeira-Garcia JL, Guerra-Seijas MJ, Gonzalez F, Perez R, Acuna C, 1990 Location of neurons projecting to the retina in mammals. Neurosci Res 8(4), 291–302. [PubMed: 2175862]

Laiginhas R, Guimaraes M, Cardoso P, Santos-Sousa H, Preto J, Nora M, Chibante J, Falcao-Reis F, Falcao M, 2019 Retinal Nerve Fiber Layer Thickness Decrease in Obesity as a Marker of Neurodegeneration. Obes Surg.

Lavoie J, Hebert M, Beaulieu JM, 2014a Glycogen synthase kinase-3 overexpression replicates electroretinogram anomalies of offspring at high genetic risk for schizophrenia and bipolar disorder. Biol Psychiatry 76(2), 93–100. [PubMed: 24138923]

Lavoie J, Illiano P, Sotnikova TD, Gainetdinov RR, Beaulieu JM, Hebert M, 2014b The electroretinogram as a biomarker of central dopamine and serotonin: potential relevance to psychiatric disorders. Biol Psychiatry 75(6), 479–486. [PubMed: 23305992]

Lavoie J, Maziade M, Hebert M, 2014c The brain through the retina: the flash electroretinogram as a tool to investigate psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry 48, 129–134. [PubMed: 24121062]

Lecleire-Collet A, Audo I, Aout M, Girmens JF, Sofroni R, Erginay A, Le Gargasson JF, Mohand-Said S, Meas T, Guillausseau PJ, Vicaut E, Paques M, Massin P, 2011 Evaluation of retinal function and flicker light-induced retinal vascular response in normotensive patients with diabetes without retinopathy. Invest Ophthalmol Vis Sci 52(6), 2861–2867. [PubMed: 21282578]

Lee MS, Fern AI, 2004 Fluphenazine and its toxic maculopathy. Ophthalmic research 36(4), 237–239. [PubMed: 15292663]

Lee WW, Tajunisah I, Sharmilla K, Peyman M, Subrayan V, 2013 Retinal nerve fiber layer structure abnormalities in schizophrenia and its relationship to disease state: evidence from optical coherence tomography. Invest Ophthalmol Vis Sci 54(12), 7785–7792. [PubMed: 24135757]

Lewine R, Martin M, Hart M, 2017 Sex versus gender differences in schizophrenia: The case for normal personality differences. Schizophr Res 189, 57–60. [PubMed: 28215470]

Lindenmayer JP, Bernstein-Hyman R, Grochowski S, 1994 A new five factor model of schizophrenia. Psychiatr Q 65(4), 299–322. [PubMed: 7831416]

Lindenmayer JP, Grochowski S, Hyman RB, 1995 Five factor model of schizophrenia: replication across samples. Schizophr Res 14(3), 229–234. [PubMed: 7766534]

Linsker R, 1988 Self-organization in a perceptual network. IEEE Computer, 105–117.

Liu D, Zhang L, Li Z, Zhang X, Wu Y, Yang H, Min B, Zhang X, Ma D, Lu Y, 2015 Thinner changes of the retinal nerve fiber layer in patients with mild cognitive impairment and Alzheimer's disease. BMC neurology 15, 14. [PubMed: 25886372]

Lizano P, Bannai D, Lutz O, Kim L, Miller J, Keshavan M, in press A meta-analysis of retinal cytoarchitectural abnormalities in schizophrenia and bipolar disorder. Schizophrenia Bulletin.

Lucas A, Thirion A, Schwan R, Krieg J, Angioi-Duprez K, Laprevote V, Schwitzer T, 2019 Association between increased retinal background noise and co-occurrent regular cannabis and alcohol use. Prog Neuropsychopharmacol Biol Psychiatry 89, 335–340. [PubMed: 30292729]

Ma S, Hangya B, Leonard CS, Wisden W, Gundlach AL, 2018 Dual-transmitter systems regulating arousal, attention, learning and memory. Neurosci Biobehav Rev 85, 21–33. [PubMed: 28757457]

Mamakou V, Thanopoulou A, Gonidakis F, Tentolouris N, Kontaxakis V, 2018 Schizophrenia and type 2 diabetes mellitus. Psychiatriki 29(1), 64–73. [PubMed: 29754122]

Mangun GR, Hansen JC, Hillyard SA, 1986 Electroretinograms reveal no evidence for centrifugal modulation of retinal inputs during selective attention in man. Psychophysiology 23(2), 156–165. [PubMed: 3704071]

Marmor MF, Hock P, Schechter G, Pfefferbaum A, Berger PA, Maurice R, 1988 Oscillatory potentials as a marker for dopaminergic disease. Documenta ophthalmologica. Advances in ophthalmology 69(3), 255–261. [PubMed: 3048944]

McDaid TM, Smyth S, 2015 Metabolic abnormalities among people diagnosed with schizophrenia: a literature review and implications for mental health nurses. Journal of psychiatric and mental health nursing 22(3), 157–170. [PubMed: 25524393]

Meier MH, Gillespie NA, Hansell NK, Hewitt AW, Hickie IB, Lu Y, McGrath J, MacGregor S, Medland SE, Sun C, Wong TY, Wright MJ, Zhu G, Martin NG, Mackey DA, 2015 Retinal microvessels reflect familial vulnerability to psychotic symptoms: A comparison of twins discordant for psychotic symptoms and controls. Schizophr Res.

Meier MH, Shalev I, Moffitt TE, Kapur S, Keefe RS, Wong TY, Belsky DW, Harrington H, Hogan S, Houts R, Caspi A, Poulton R, 2013 Microvascular abnormality in schizophrenia as shown by retinal imaging. Am J Psychiatry 170(12), 1451–1459. [PubMed: 24030514]

Mendrek A, Mancini-Marie A, 2016 Sex/gender differences in the brain and cognition in schizophrenia. Neurosci Biobehav Rev 67, 57–78. [PubMed: 26743859]

Meredith TA, Aaberg TM, Willerson WD, 1978 Progressive chorioretinopathy after receiving thioridazine. Arch Ophthalmol 96(7), 1172–1176. [PubMed: 666624]

Miller GA, Chapman JP, 2001 Misunderstanding analysis of covariance. J Abnorm Psychol 110(1), 40–48. [PubMed: 11261398]

Minassian A, Granholm E, Verney S, Perry W, 2004 Pupillary dilation to simple vs. complex tasks and its relationship to thought disturbance in schizophrenia patients. Int J Psychophysiol 52(1), 53–62. [PubMed: 15003372]

Modi P, Arsiwalla T, 2018 Hypertensive Retinopathy, StatPearls, Treasure Island (FL).

Moghimi P, Jiminez NT, McLoon LK, Netoff TI, Lee MS, MacDonald AW 3rd, Miller RF, in press Electroretinographic evidence of retinal ganglion cell-dependent function in schizophrenia. Schizophrenia Research.

Morra LF, Strauss GP, 2016 Severity of hypertension predicts the generalized neurocognitive deficit in schizophrenia. Schizophr Res 176(2–3), 527–528. [PubMed: 27397721]

Nasser JA, Del Parigi A, Merhige K, Wolper C, Geliebter A, Hashim SA, 2013 Electroretinographic detection of human brain dopamine response to oral food stimulation. Obesity (Silver Spring) 21(5), 976–980. [PubMed: 23784899]

Neves MS, Jordon K, Dragt H, 1990 Extensive chorioretinopathy associated with very low dose thioridazine. Eye 4 (Pt 5), 767–770. [PubMed: 2282954]

Nishanth KN, Chadda RK, Sood M, Biswas A, Lakshmy R, 2017 Physical comorbidity in schizophrenia & its correlates. Indian J Med Res 146(2), 281–284. [PubMed: 29265031]

Ong YT, Hilal S, Cheung CY, Venketasubramanian N, Niessen WJ, Vrooman H, Anuar AR, Chew M, Chen C, Wong TY, Ikram MK, 2015 Retinal neurodegeneration on optical coherence tomography and cerebral atrophy. Neurosci Lett 584, 12–16. [PubMed: 25451722]

Ooto S, Hangai M, Tomidokoro A, Saito H, Araie M, Otani T, Kishi S, Matsushita K, Maeda N, Shirakashi M, Abe H, Ohkubo S, Sugiyama K, Iwase A, Yoshimura N, 2011 Effects of age, sex, and axial length on the three-dimensional profile of normal macular layer structures. Invest Ophthalmol Vis Sci 52(12), 8769–8779. [PubMed: 21989721]

Ortiz G, Odom JV, Passaglia CL, Tzekov RT, 2017 Efferent influences on the bioelectrical activity of the retina in primates. Documenta ophthalmologica. Advances in ophthalmology 134(1), 57–73. [PubMed: 28032236]

Pan J, Zhou Y, Xiang Y, Yu J, 2018 Retinal nerve fiber layer thickness changes in Schizophrenia: A meta-analysis of case-control studies. Psychiatry Res 270, 786–791. [PubMed: 30551326]

Parfenov VA, Ostroumova capital Te CEMC, Ostroumova OD, Pavleyva EE, 2018 Features of the clinical picture in patients of middle age with essential hypertension. Ter Arkh 90(9), 15–26.

Parisi V, Uccioli L, 2001 Visual electrophysiological responses in persons with type 1 diabetes. Diabetes Metab Res Rev 17(1), 12–18. [PubMed: 11241887]

Perlman I, 2012 The electroretinogram: ERG, in: Kolb H, Nelson R, Fernandez E, Jones B (Eds.), Webvision: The organization of the retina and visual system.

Phillipson OT, Harris JP, 1985 Perceptual changes in schizophrenia: a questionnaire survey. Psychol Med 15(4), 859–866. [PubMed: 4080889]

Popova E, 2014 Role of dopamine in distal retina. J Comp Physiol A Neuroethol Sens Neural Behav Physiol 200(5), 333–358. [PubMed: 24728309]

Popova E, Kostov M, Kupenova P, 2016 Effects of dopamine D1 receptor blockade on the ERG b- and d-waves during blockade of ionotropic GABA receptors. Eye Vis (Lond) 3, 32. [PubMed: 27981058]

Porciatti V, 2015 Electrophysiological assessment of retinal ganglion cell function. Experimental eye research 141, 164–170. [PubMed: 25998495]

Qualls-Creekmore E, Yu S, Francois M, Hoang J, Huesing C, Bruce-Keller A, Burk D, Berthoud HR, Morrison CD, Munzberg H, 2017 Galanin-Expressing GABA Neurons in the Lateral Hypothalamus Modulate Food Reward and Noncompulsive Locomotion. J Neurosci 37(25), 6053–6065. [PubMed: 28539422]

Ravalico G, Rinaldi G, Solimano N, Bellini G, Cosenzi A, Sacerdote A, Bocin E, 1995 Oscillatory potentials in subjects with treated hypertension. Ophthalmologica 209(4), 187–189. [PubMed: 8545090]

Reimer J, McGinley MJ, Liu Y, Rodenkirch C, Wang Q, McCormick DA, Tolias AS, 2016 Pupil fluctuations track rapid changes in adrenergic and cholinergic activity in cortex. Nature communications 7, 13289.

Rosso M, Kimbrough DJ, Gonzalez CT, Glanz BI, Healy BC, Rocca MA, Filippi M, Weiner H, Chitnis T, 2019 Cross-sectional study of smoking exposure: no differential effect on OCT metrics in a cohort of MS patients. Mult Scler J Exp Transl Clin 5(1), 2055217319828400.

Roy M, Roy A, Williams J, Weinberger L, Smelson D, 1997 Reduced blue cone electroretinogram in cocaine-withdrawn patients. Arch Gen Psychiatry 54(2), 153–156. [PubMed: 9040283]

Roy M, Smelson DA, Roy A, 1996 Abnormal electroretinogram in cocaine-dependent patients. Relationship to craving. Br J Psychiatry 168(4), 507–511. [PubMed: 8730949]

Ryoo NK, Ahn SJ, Park KH, Ahn J, Seo J, Han JW, Kim KW, Woo SJ, 2018 Thickness of retina and choroid in the elderly population and its association with Complement Factor H polymorphism: KLoSHA Eye study. PLoS One 13(12), e0209276. [PubMed: 30596689]

Samani NN, Proudlock FA, Siram V, Suraweera C, Hutchinson C, Nelson CP, Al-Uzri M, Gottlob I, 2018 Retinal Layer Abnormalities as Biomarkers of Schizophrenia. Schizophr Bull 44(4), 876–885. [PubMed: 29272501]

Sanchez-Villarejo MV, Lopez-Pedrajas R, Sanchez-Vallejo V, Genoves JM, Muriach M, Barcia JM, Romero FJ, Miranda M, 2014 Chronic cocaine effects in retinal metabolism and electrophysiology: treatment with topiramate. Current eye research 39(5), 493–503. [PubMed: 24215266]

Sancho-Tello M, Muriach M, Barcia J, Bosch-Morell F, Genoves JM, Johnsen-Soriano S, Romero B, Almansa I, Diaz-Llopis M, Garcia-Delpech S, Roma J, Romero FJ, 2008 Chronic alcohol feeding induces biochemical, histological, and functional alterations in rat retina. Alcohol Alcohol 43(3), 254–260. [PubMed: 18304993]

Satue M, Seral M, Otin S, Alarcia R, Herrero R, Bambo MP, Fuertes MI, Pablo LE, Garcia-Martin E, 2014 Retinal thinning and correlation with functional disability in patients with Parkinson's disease. The British journal of ophthalmology 98(3), 350–355. [PubMed: 24276697]

Schechter G, Hock P, Rodgers K, Pfefferbaum A, Marmor MF, Berger PA, 1987 Electroretinographic assessment in schizophrenia. Electroencephalogr Clin Neurophysiol Suppl 40, 746–751.

Schlosser DA, Fisher M, Gard D, Fulford D, Loewy RL, Vinogradov S, 2014 Motivational deficits in individuals at-risk for psychosis and across the course of schizophrenia. Schizophr Res 158(1–3), 52–57. [PubMed: 25008792]

Schonfeldt-Lecuona C, Kregel T, Schmidt A, Kassubek J, Dreyhaupt J, Freudenmann RW, Connemann BJ, Gahr M, Pinkhardt EH, 2019 Retinal single-layer analysis with optical coherence tomography (OCT) in schizophrenia spectrum disorder. Schizophr Res.

Schonfeldt-Lecuona C, Kregel T, Schmidt A, Pinkhardt EH, Lauda F, Kassubek J, Connemann BJ, Freudenmann RW, Gahr M, 2016 From Imaging the Brain to Imaging the Retina: Optical Coherence Tomography (OCT) in Schizophrenia. Schizophr Bull 42(1), 9–14. [PubMed: 26048298]

Schwitzer T, Schwan R, Albuisson E, Giersch A, Lalanne L, Angioi-Duprez K, Laprevote V, 2017 Association Between Regular Cannabis Use and Ganglion Cell Dysfunction. JAMA Ophthalmol 135(1), 54–60. [PubMed: 27930757]

Schwitzer T, Schwan R, Angioi-Duprez K, Giersch A, Lalanne L, Albuisson E, Laprevote V, 2018 Delayed bipolar and ganglion cells neuroretinal processing in regular cannabis users: The retina as a relevant site to investigate brain synaptic transmission dysfunctions. J Psychiatr Res 103, 75–82. [PubMed: 29783078]

Schwitzer T, Schwan R, Bernardin F, Jeantet C, Angioi-Duprez K, Laprevote V, 2016 Commentary: Anatomical constitution of sense organs as a marker of mental disorders. Frontiers in behavioral neuroscience 10, 56. [PubMed: 27047357]

Sedighi B, Shafa MA, Abna Z, Ghaseminejad AK, Farahat R, Nakhaee N, Hassani N, 2014 Association of cognitive deficits with optical coherence tomography changes in multiple sclerosis patients. Journal of Multiple Sclerosis 1.

Seidman LJ, Mirsky AF, 2017 Evolving Notions of Schizophrenia as a Developmental Neurocognitive Disorder. Journal of the International Neuropsychological Society : JINS 23(9–10), 881–892. [PubMed: 29198285]

Silverstein SM, 2016 Visual Perception Disturbances in Schizophrenia: A Unified Model. Nebr Symp Motiv 63, 77–132. [PubMed: 27627825]

Silverstein SM, Demmin D, Bednar JA, 2017a Computational modeling of contrast sensitivity and orientation tuning in first-episode and chronic schizophrenia. Computational Psychiatry 1, 102–131. [PubMed: 30090855]

Silverstein SM, Demmin D, Skodlar B, 2017b Space and Objects: On the Phenomenology and Cognitive Neuroscience of Anomalous Perception in Schizophrenia (Ancillary Article to EAWE Domain 1). Psychopathology 50(1), 60–67. [PubMed: 28073112]

Silverstein SM, Keane BP, 2011 Vision Science and Schizophrenia Research: Toward a Review of the Disorder Editors' Introduction to Special Section. Schizophr Bull 37(4), 681–689. [PubMed: 21700588]

Silverstein SM, Paterno D, Cherneski L, Green S, 2018 Optical coherence tomography indices of structural retinal pathology in schizophrenia. Psychol Med 48(12), 2023–2033. [PubMed: 29233210]

Silverstein SM, Rosen R, 2015 Schizophrenia and the eye. Schizophrenia Research: Cognition 2(2), 46–55.

Silverstein SM, Wibral M, Phillips WA, 2017c Implications of information theory for computational modeling of schizophrenia. Computational Psychiatry 1, 82–101. [PubMed: 29601053]

Spaide RF, 2019 Measurable Aspects Of The Retinal Neurovascular Unit In Diabetes, Glaucoma And Controls. Am J Ophthalmol.

Strauss GP, Waltz JA, Gold JM, 2014 A review of reward processing and motivational impairment in schizophrenia. Schizophr Bull 40 Suppl 2, S107–116. [PubMed: 24375459]

Su D, Robson AG, Xu D, Lightman S, Sarraf D, 2017 Quinine Toxicity: Multimodal Retinal Imaging and Electroretinography Findings. Retin Cases Brief Rep 11 Suppl 1, S102–S106. [PubMed: 27662234]

Subramaniam K, Hooker CI, Biagianti B, Fisher M, Nagarajan S, Vinogradov S, 2015 Neural signal during immediate reward anticipation in schizophrenia: Relationship to real-world motivation and function. NeuroImage. Clinical 9, 153–163. [PubMed: 26413478]

Teberik K, 2019 The Effect of Smoking on Macular, Choroidal, and Retina Nerve Fiber Layer Thickness. Turk J Ophthalmol 49(1), 20–24. [PubMed: 30829021]

Tega Y, Kubo Y, Yuzurihara C, Akanuma S, Hosoya K, 2015 Carrier-Mediated Transport of Nicotine Across the Inner Blood-Retinal Barrier: Involvement of a Novel Organic Cation Transporter Driven by an Outward H(+) Gradient. J Pharm Sci 104(9), 3069–3075. [PubMed: 25892000]

Thakkar KN, Brascamp JW, Ghermezi L, Fifer K, Schall JD, Park S, 2018 Reduced pupil dilation during action preparation in schizophrenia. Int J Psychophysiol 128, 111–118. [PubMed: 29574231]

Theisen FM, Linden A, Geller F, Schafer H, Martin M, Remschmidt H, Hebebrand J, 2001 Prevalence of obesity in adolescent and young adult patients with and without schizophrenia and in relationship to antipsychotic medication. J Psychiatr Res 35(6), 339–345. [PubMed: 11684141]

Tian T, Zhu XH, Liu YH, 2011 Potential role of retina as a biomarker for progression of Parkinson's disease. International journal of ophthalmology 4(4), 433–438. [PubMed: 22553695]

Tong JY, Pai A, Heydon P, Young SH, 2017 Clozapine-induced maculopathy. The Medical journal of Australia 206(6), 246. [PubMed: 28359003]

Topcu-Yilmaz P, Aydin M, Ilhan BC, 2018 Evaluation of retinal nerve fiber layer, macular, and choroidal thickness in schizophrenia: spectral optic coherence tomography findings. Psychiatry and Clinical Psychopharmacology 29(1).

Torrealba F, Riveros ME, Contreras M, Valdes JL, 2012 Histamine and motivation. Frontiers in systems neuroscience 6, 51. [PubMed: 22783171]

Toyonaga N, Adachi-Usami E, Yamazaki H, 1989 Clinical and electrophysiological findings in three patients with toluene dependency. Documenta ophthalmologica. Advances in ophthalmology 73(2), 201–207. [PubMed: 2638629]

Tyrberg M, Lindblad U, Melander A, Lovestam-Adrian M, Ponjavic V, Andreasson S, 2011 Electrophysiological studies in newly onset type 2 diabetes without visible vascular retinopathy. Documenta ophthalmologica. Advances in ophthalmology 123(3), 193–198. [PubMed: 22057379]

Ucar D, Yildiz N, Hepokur M, Baltu F, Guliyev E, Emul M, Sarici AM, 2018 Retinal Nerve Fiber Layer Thickness Alterations after Electroconvulsive Therapy in Patients with Mental Illness. Semin Ophthalmol 33(7–8), 852–857. [PubMed: 30351990]

Uribe-Cerda S, Morselli E, Perez-Leighton C, 2018 Updates on the neurobiology of food reward and their relation to the obesogenic environment. Curr Opin Endocrinol Diabetes Obes 25(5), 292–297. [PubMed: 30063551]

Varghese SB, Reid JC, Hartmann EE, Keyser KT, 2011 The effects of nicotine on the human electroretinogram. Invest Ophthalmol Vis Sci 52(13), 9445–9451. [PubMed: 22064991]

Verney SP, Granholm E, Marshall SP, 2004 Pupillary responses on the visual backward masking task reflect general cognitive ability. Int J Psychophysiol 52(1), 23–36. [PubMed: 15003370]

Vila A, Satoh H, Rangel C, Mills SL, Hoshi H, O'Brien J, Marshak DR, Macleish PR, Marshak DW, 2012 Histamine receptors of cones and horizontal cells in Old World monkey retinas. J Comp Neurol 520(3), 528–543. [PubMed: 21800315]

Vincent M, Zemon V, Nolan R, Balcer L, Goff D, Hasenaj L, Worthington M, Butler P, in press Optical coherence tomography of the retina in schizophrenia: Inter-device reliability and relationships with perceptual function. Schizophrenia Research.

Wachtmeister L, 1998 Oscillatory potentials in the retina: what do they reveal. Prog Retin Eye Res 17(4), 485–521. [PubMed: 9777648]

Wang Z, Zou Y, Li W, Wang X, Zhang M, Wang W, 2015 Application of Optical Coherence Tomography and Contrast Sensitivity Test for Observing Fundus Changes of Patients With Pregnancy-Induced Hypertension Syndrome. Medicine (Baltimore) 94(44), e1641. [PubMed: 26554764]

Warner R, Laugharne J, Peet M, Brown L, Rogers N, 1999 Retinal function as a marker for cell membrane omega-3 fatty acid depletion in schizophrenia: a pilot study. Biol Psychiatry 45(9), 1138–1142. [PubMed: 10331105]

Waters F, Collerton D, Ffytche DH, Jardri R, Pins D, Dudley R, Blom JD, Mosimann UP, Eperjesi F, Ford S, Laroi F, 2014 Visual hallucinations in the psychosis spectrum and comparative information from neurodegenerative disorders and eye disease. Schizophr Bull 40 Suppl 4, S233–245. [PubMed: 24936084]

Williams JM, Gandhi KK, 2008 Use of caffeine and nicotine in people with schizophrenia. Current drug abuse reviews 1(2), 155–161. [PubMed: 19630714]

Williams JM, Gandhi KK, Lu SE, Kumar S, Shen J, Foulds J, Kipen H, Benowitz NL, 2010 Higher nicotine levels in schizophrenia compared with controls after smoking a single cigarette. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 12(8), 855–859. [PubMed: 20584771]

Witkovsky P, 2004 Dopamine and retinal function. Documenta ophthalmologica. Advances in ophthalmology 108(1), 17–40. [PubMed: 15104164]

Yanovsky Y, Li S, Klyuch BP, Yao Q, Blandina P, Passani MB, Lin JS, Haas HL, Sergeeva OA, 2011 L-Dopa activates histaminergic neurons. J Physiol 589(Pt 6), 1349–1366. [PubMed: 21242252]

Yasin Alibhai A, Moult EM, Shahzad R, Rebhun CB, Moreira-Neto C, McGowan M, Lee D, Lee B, Baumal CR, Witkin AJ, Reichel E, Duker JS, Fujimoto JG, Waheed NK, 2018 Quantifying Microvascular Changes Using OCT Angiography in Diabetic Eyes without Clinical Evidence of Retinopathy. Ophthalmol Retina 2(5), 418–427. [PubMed: 30820483]

Yilmaz U, Kucuk E, Ulgen A, Ozkose A, Demircan S, Ulusoy DM, Zararsiz G, 2016 Retinal nerve fiber layer and macular thickness measurement in patients with schizophrenia. Eur J Ophthalmol 26(4), 375–378. [PubMed: 26742871]

Yu JG, Feng YF, Xiang Y, Huang JH, Savini G, Parisi V, Yang WJ, Fu XA, 2014 Retinal nerve fiber layer thickness changes in Parkinson disease: a meta-analysis. PLoS One 9(1), e85718. [PubMed: 24465663]

Yu YC, Satoh H, Wu SM, Marshak DW, 2009 Histamine enhances voltage-gated potassium currents of ON bipolar cells in macaque retina. Invest Ophthalmol Vis Sci 50(2), 959–965. [PubMed: 18836167]

Zeng Y, Cao D, Yu H, Yang D, Zhuang X, Hu Y, Li J, Yang J, Wu Q, Liu B, Zhang L, in press Early retinal neurovascular involvement in patients with diabetes without clinically detectable retinopathy. British Journal of Ophthalmology.

Zilliox LA, Chadrasekaran K, Kwan JY, Russell JW, 2016 Diabetes and Cognitive Impairment. Curr Diab Rep 16(9), 87. [PubMed: 27491830]

Zimmerman H, Oberwahrenbrock T, Brandt AU, Paul F, Dörr J, 2014 Optical coherence tomography for retinal imaging in multiple sclerosis. Degenerative Neurological and Neuromuscular Disease 4, 153–162.